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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,481	12/18/2001	Miquel Sales Amill	INL-048	3281

22832 7590 02/15/2007

Kirkpatrick & Lockhart Preston Gates Ellis LLP
STATE STREET FINANCIAL CENTER
One Lincoln Street
BOSTON, MA 02111-2950

EXAMINER	
DAVIS, DEBORAH A	
ART UNIT	**PAPER NUMBER**
1655	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/022,481	SALES AMILL ET AL.	
	Examiner	Art Unit	
	Deborah A. Davis	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-18,20-22,32,34 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-18,20-22,32,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The petition filed July 19, 2005 is acknowledged and approved. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn. Currently, claims 1-22 and 32, 34-35 are pending and under consideration for examination. Claims 1 and 18 are amended and 34-35 are newly added. Claims 4, 19, 23-31 and 33 are cancelled.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 9 and 18 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claims 9 and 18 recite C4BP protein or a fragment thereof is vague because it is unclear as to what this structure entails.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 9 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the C4BP protein, does not reasonably provide enablement for a fragment of the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The fragment structure of the C4BP fragment is unknown. Although it is within the skill of the artisan to make produce fragments of proteins, one of ordinary skill in the art would not know how to use the C4BP fragment without knowing its structure and function. The specification provides a general teaching of various "fragments" of proteins and antibodies but does not define the structure of those fragments. Since an amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similarity activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984", (page 315) teaches that variation of the primary structure of a protein can result in an unstable molecule. He teaches that a single amino acid change can cause lower stabilities (page 315). Therefore, it would be undue experimentation to predict which part of the fragment would retain its affinity without structure information.

There is no guidance provided in the specification as to how one would begin to make or use "fragments of the C4BP protein". The specification does not support the broad scope of the claims, which encompass all modifications of fragments because the specification does not disclose the following:

> What fragments can be made which can retain the biological activity of the intact protein; the specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying some of the factors above, the above test to the fact of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount if experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other fragments of proteins having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high. One of skill in the art would require guidance in order to make or use fragments of C4BP proteins in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 7, and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Cambiaso et al (USP#4,184,849).

The reference of Cambiaso et al teaches a mixed agglutination assay to detect antigens or antibodies qualitatively and quantitatively (abstract). The quantitative method comprises assaying a particular Ag or Ab in a liquid sample, wherein a first particulate reagent comprising a solid particulate support material carrying a first substance and a second particulate reagent comprising a solid particulate support material carrying a second substance (column 1, lines 48-66). The examiner interprets the Ag or Ab as the first member. The examiner interprets the first particulate reagent as a first particle bound to a second member as recited in claim 1, steps (a) & (b). The second particulate reagent is interpreted as the second particle bound to a third member as recited in step (c). The first particulate reagent is capable of binding to the particular Ag or Ab (column 1, lines 60-68) which will form a first complex as recited in step (b). Two different particulate reagents are used in the assay (column 2, lines 9-12). The assay can be performed competitively wherein the first and second particulate reagents and the Ag or Ab compete for binding (column 1, lines 20-23 and column 8,

lines 28-35). This teaching satisfies the limitation of step (c) wherein the third member is also capable of binding to the first member as recited in step (c) to form a second complex as recited in step (d) and claim 11. The extent of agglutination or non-agglutination of particulate reagents is measured thereby determining the amount of Ag or Ab present in the sample (column 2, lines 1-8) as recited in step (e). The first reagent particles that do not bind to the Ag or Ab (unbound form) in the sample will agglutinate with the second reagent particles and will be measured by particle counting (column 4, lines 32-37) or by measuring increases in turbidity (column 6, Table 3) as recited in step (e). With respect to claim 2, both particulate reagents of the assay can be antibodies (column 3, lines 1-15). With respect to claim 3, latex beads are used (column 2, lines 67-68). With respect to claim 7, the assay is performed quantitatively (abstract).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 5-6, 8-9, 13,18, 20-22, 32 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cambiaso et al in view of Koike et al (USP#5,187,067).

The teachings of Cambiaso et al are set forth above and differ from the instant claims in not teaching a composition or protein S and C4b-binding protein.

Although the Cambiaso et al reference does not specifically recite a composition, the components of the composition as recited in claim 18 are taught by the instant reference of Cambiaso, with the exception of protein S and the second member C4BP.

However, Koike et al teaches immunological determination of free human protein S and C4BP-protein S complex in a sandwich format utilizing monoclonal antibodies affixed to insoluble latex carriers (abstract). This method of detection permit measurement of free human protein S or C4bp-protein S complex in an assay sample (i.e. plasma) with good accuracy without variations in the quality of reagents. Protein S and C4bp-protein S complex can be measured directly, and accurate measurement within short periods of time. The determination methods of this invention permit diagnosis of the conditions of thrombosis having cancer as a basic disease, nephrosis and accurate determination of fibrinolytic state of toxemia of pregnancy (column 3, lines 1-35). Plasma samples were taken from normal healthy subject as well who did not exhibit disease and patients who did (column 15, lines 1-12). Protein S and C4BP-

protein S complexes were compared and measured (column 15, lines 15-55). These assays can be formed in a two-step method (sequentially) comprising contacting the sample with the fixed primary antibody and then a second antibody or by a one-step method the secondary antibody simultaneously with the primary antibody (column 4, lines 32-68). With respect to claim 13 that recites that step (b) of claim 1 is performed within 0 to about 180 seconds is an obvious modification of the prior art already taught by Cambaiso. Cambaiso teaches step (b) but didn't recite the time the time it took to perform this step. It is the examiner position that this step is mere optimization and is within the skill of the artisan to perform, especially since it has long been held to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. At 458, 105 USPQ at 236-237. The "discover of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Voesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). The reference of Cambiaso teach difference size particles as recited in claims 34-35: The particulate reagents used in the method of the invention are of microscopic or sub-microscopic size, i.e. they will generally be smaller than 15 microns and most usually of the order of a few microns or sub-micron in

size. Latex particles of such sizes are commercially available. It is known to bind Ab or Ag to microscopic particulate material such as latex. This teaching appear to meet the limitation of claim 34-35, which recite particle ranges from about 50nm to about 1000 nm (column 2, lines 53-58).

It would have been obvious to one of ordinary skill in the art to modify the agglutination assay of Cambiaso et al to include an assay composition for the detection of protein S and its C4b-binding protein as taught by Koike et al because it offers great advantages to medicine wherein determination of these proteins can permit diagnosis of conditions related to cancer and toxemia in pregnant patients

11. Claims 12, and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cambiaso et al in view of Mischak et al (USP#6,124,430).

The teachings of Cambiaso et al are set forth above and differ in the instant claims in not teaching molar ratios.

However, Mischak et al teaches immunoassays to quantify protein levels in plasma, serum and whole blood. The assay can be carried out either in a sandwich or competition format (column 7, lines 20-45). In a sandwich type assay, the antibody is normally employed in amounts substantially in molar excess of the maximum amount of protein expected to be in the sample (column 8, lines 1-10). Preferably, the antibodies chosen to carry out the sandwich type assay are selected such that the first antibody, which is brought into contact with the protein in the sample, does not bind all or part of

the epitope recognized by the second antibody, thereby significantly interfering with the ability of the second antibody to bind the protein.

It would have been obvious to one of ordinary skill in the art to modify the teachings of Cambiaso et al to include molar ratios taught by Mischak et al because it is known in the art that when sandwich assays are utilized, different antibodies in molar access such as monoclonal and polyclonal are selected so that both antibodies recognizing the same epitopes with a range in close proximity will not overlap (column 7, lines 20-52).

12. Claims 18, 20-22 rejected under 35 U.S.C. 103(a) as being unpatentable over Cambiaso et al in view of Koike et al and in further view of Zuk et al (USP#4,281,061) ***to address the kit claims.***

The teachings of Cambiaso et al in view of Koike et al are set forth above and differ from the instant claims in not teaching a kit.

Although the Cambiaso et al in view of Koike et al does not specifically recite a kit, the components of the kit as recited in claim 18 are taught by the instant references of Cambiaso in view of Koike.

However, Zuk teach that "as a matter of convenience the reagents [of an immunoassay} can be provided as kits, where the reagents are in predetermined ratios, so as to substantially optimize the sensitivity of the assay in the range of interest" (column 22, lines 63-66).

It would have been obvious to one of ordinary skill in the art at the time of applicant's invention to take the components assay components of Cambiaso in view of Koike et al and format them into a kit because Zuk teach that is convenient to do so and one can enhance sensitivity of a method by providing reagents as a kit. One would be motivated to do so to eliminate the variability that can occur when performing the assay.

Conclusion

No claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah A. Davis whose telephone number is (571) 272-0818. The examiner can normally be reached on 8-5 Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Davis Deborah can be reached on (571) 272-0818. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Deborah A. Davis
Patent Examiner
June 1, 2006

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
6/09/06